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Dated 10 September 1999.

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11NOV98 E403596-1 D00524
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Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your reference — 4-30707/P1

2. Patent application number *(The Patent Office will fill in this part)* — 10 NOV 1998 — 9824579.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NOVARTIS AG
Schwarzwaldallee 215
4058 Basel

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Switzerland — 07125487002

4. Title of the invention — Organic Compounds

5. Name of your agent *(if you have one)* — B. A. Yorke & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Coomb House
7 St. John's Road
Isleworth, Middlesex TW7 6NH

Patents ADP number *(if you know it)* — 1800001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from a earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

Patents Form 1/77

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Continuation sheets of this form	
Description	42
Claim(s)	5
Abstract	
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10. If you are also filing any of the following, state how many against each items.

Priority documents	-
Translations of priority documents	-
Statemtent of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	yes
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. B.A Yorke & Co.

I/We request the grant of a patent on the basis of this application.

Signature B. A. Yorke & Co. Date: 9th November 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs E Cheetham
0181 560 5847

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Notes

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Organic Compounds

The invention relates to new benzamide derivatives, processes for the preparation thereof, the application thereof in a process for the treatment of the human or animal body, the use thereof – alone or in combination with one or more other pharmaceutically active compounds – for the treatment especially of a proliferative disease, such as a tumor disease, a method for the treatment of such disease in animals, especially in humans, and the use of such a compound – alone or in combination with one or more other pharmaceutically active compounds – for manufacture of a pharmaceutical preparation (medicament) for the treatment especially of a proliferative disease, such as a tumor.

Background of the invention

Certain diseases are known to be associated with deregulated angiogenesis, for example retinopathies, psoriasis, haemangioblastoma, haemangioma, and neoplastic diseases (solid tumors).

According to recent findings, at the centre of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as "Vascular Endothelial Growth Factor" (=VGEF), along with its cellular receptors (see Breier, G., et al., Trends in Cell Biology 6, 454-6 [1996] and references cited therein).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein and is related to "Platelet-Derived Growth Factor" (PDGF). It is produced by normal cell lines and tumor cell lines, is an endothelial cell-specific mitogen, shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea), is chemotactic for endothelial cells and monocytes, and induces plasminogen activators in endothelial cells, which are then involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placenta Growth Factor" (PLGF) and VEGF-C.

VEGF receptors are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, e.g. VEGFR-1, VEGFR-2, and VEGFR-3.

A large number of human tumors, especially gliomas and carcinomas, express high levels of VEGF and its receptors. This has led to the hypothesis that the VEGF released by tumor cells could stimulate the growth of blood capillaries and the proliferation of tumor endothelium in a paracrine manner and thus, through the improved blood supply, accelerate tumor growth. Increased VEGF expression could explain the occurrence of cerebral oedema in patients with glioma. Direct evidence of the role of VEGF as a tumor angiogenesis factor *in vivo* has been obtained from studies in which VEGF expression or VEGF activity was inhibited. This was achieved with antibodies which inhibit VEGF activity, with dominant-negative VEGFR-2 mutants which inhibited signal transduction, or with the use of antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumor cell lines *in vivo* as a result of inhibited tumor angiogenesis.

Angiogenesis is regarded as an absolute prerequisite for those tumors which grow beyond a maximum diameter of about 1–2 mm; up to this limit, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) Inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved between apoptosis and proliferation; 2) Prevention of the migration of tumor cells owing to the absence of bloodflow to and from tumors; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels.

Summary of the invention

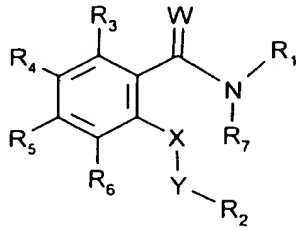
Surprisingly, it has now been found that benzamide derivatives of formula I, described below, are a new class of compounds that have advantageous pharmacological properties and

inhibit, for example, the activity of the VEGF receptor tyrosine kinase and the growth of tumors.

The compounds of formula I open up, for example, an unexpected new therapeutic approach, especially for diseases in the treatment of which, and also for the prevention of which, an inhibition of angiogenesis and/or of the VEGF receptor tyrosine kinase shows beneficial effects.

Full description of the invention

The invention relates to compounds of formula I,



(I)

wherein

W is O or S;

X is NR_8;

Y is CHR_9-$(CH_2)_n$ wherein

R_9 is hydrogen or lower alkyl, and

n is an integer of from and including 0 to and including 3;

or Y is C=O or SO_2;

R_1 is aryl or heteroaryl

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or salts thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially

up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms (for example in compounds of formula I, wherein R_9 is lower alkyl) may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl or isobutyl, propyl, such as n-propyl or isopropyl, ethyl or preferably methyl.

The index n is preferably 0 or 1, especially 0.

A is especially branched or preferably linear C_1-C_4alkylene, especially methylene (CH_2), ethylene (CH_2-CH_2), trimethylene (CH_2-CH_2-CH_2) or tetramethylene (CH_2-CH_2-CH_2-CH_2), or is $CH(CH_3)$-CH_2. A is preferably methylene.

Y is preferably methylene (CH_2).

In a preferred embodiment, aryl is an aromatic radical having 6 to 14 carbon atoms, especially phenyl, naphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, lower alkylthio, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, lower alkenyl, lower alkanoyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl, dihydroxybora (-

$B(OH)_2$), heterocyclyl, and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy; aryl is preferably phenyl which is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; lower alkyl, especially methyl or also ethyl or propyl; halogen-lower alkyl, especially trifluoromethyl; lower alkylsulfinyl, such as methylsulfinyl, and lower alkanesulfonyl, such as methane sulfonyl. Aryl is preferably 3- or 4-chlorophenyl, 3-bromophenyl, 3- or 4-methylphenyl, 3- or 4-tert-butylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 4-chloro-3-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 4-methylsulfinylphenyl, 4-methanesulfonylphenyl or 2,1,3-benzodiazolyl.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; phenyl-lower alkyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl; and phenyl-lower alkoxycarbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, and carbamoyl; and is preferably N-lower alkylamino, such as N-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino, phenyl-lower alkylamino, such as benzylamino, N,N-di-lower alkylamino, N-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

In the preferred embodiment, alkyl has up to a maximum of 12 carbon atoms and is especially lower alkyl, especially methyl, or also ethyl, n-propyl, isopropyl, or tert-butyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

Etherified hydroxy is especially C_8-C_{20}alkyloxy, such as n-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropyloxy, or n-pentyloxy, phenyl-lower alkoxy, such as benzyloxy, or also phenyloxy, or as an alternative or in addition to the previous group C_8-C_{20}alkyloxy, such as n-decyloxy, halogen-lower alkoxy, such as trifluoromethyloxy or 1,1,2,2-tetrafluoroethoxy.

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as tert-butoxycarbonyloxy, or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl, or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

N-mono- or N,N-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl, and hydroxy-lower alkyl, at the terminal nitrogen atom.

Alkylphenylthio is especially lower alkylphenylthio.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

Heterocyclyl is especially a five or six-membered heterocyclic system with 1 or 2 heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl; a radical selected from 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, and 1-methyl-pyrazol-3-yl is preferred.

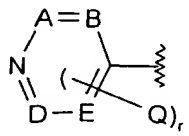
Aryl in the form of phenyl which is substituted by lower alkylene dioxy bound to two adjacent C-atoms, such as methylenedioxy, is preferably 3,4-methylenedioxyphenyl.

Heteroaryl refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula I and is preferably mono-, bi- or tricyclic, preferably mono- or bicyclic; where at least in the binding ring, but optionally also in any annealed ring, one or more, preferably 1 to 4, most preferably 3 or 4, carbon atoms are replaced each by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5 to 12, more preferably 5 to 7 ring atoms; and may be unsubstituted or substituted by one or more, especially one or two, substitutents selected from the group defined above as substitutents for aryl, most preferably by lower alkyl, such as methyl; preferably heteroaryl is selected from thienyl, furyl, pyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, lower-alkyl substituted imidazolyl, benzimidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl and furazanyl; more preferably selected from the group consisting of triazolyl, especially 1,2,4-triazolyl, 1,2,3-triazolyl or 1,3,4-triazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, indolyl, especially 3-indolyl, lower-alkylthiazolyl, especially 2-(4-methylthiazolyl), pyrrolyl, especially 1-pyrrolyl, lower alkylimidazolyl, especially 4-(1-methylimidazolyl), 4-(2-methylimidazolyl) or 4-(5-methylimidazolyl), benzimidazolyl, such as 1-benzimidazolyl, or tetrazolyl, such as 5-(1,2,3,4-tetrazolyl).

Preferably, R_1 is aryl as decribed above.

A mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms is preferably a heteroaryl group as defined above for heteroaryl, with the proviso that at least one

nitrogen is present as ring heteroatom in the binding ring (that is, the ring from which the bond starts that binds the heteroaryl moiety to the rest of the molecule). Preferred is imidazolyl, especially imidazol-4-yl, quinolyl, especially 4-quinolyl, or especially a moiety of the formula Ib



(Ib)

wherein

r is 0 to 2,

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N; preferably, each of A, B, D and E is CH; and

Q is lower alkyl, especially methyl.

Most preferably, R_2 is 4-pyridyl.

A substituent other than hydrogen is preferably selected from amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, lower alkylthio, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, lower alkenyl, lower alkanoyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl and heterocyclyl. Preferably, a substituent other than hydrogen is lower alkyl, especially methyl.

Preferably, R_3, R_4, R_5 and R_6 each are hydrogen.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for

example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

When a basic group and an acid group are present in the same molecule, a compound of formula 1 may also form internal salts.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula I have valuable pharmacological properties, as described hereinbefore and hereinafter.

The efficacy of the compounds of the invention as inhibitors of VEGF-receptor tyrosine kinase activity can be demonstrated as follows:

Test for activity against VEGF-receptor tyrosine kinase. The test is conducted using Flt-1 VEGF-receptor tyrosine kinase. The detailed procedure is as follows: 30 µl kinase solution (10 ng of the kinase domain of Flt-1, Shibuya et al., Oncogene 5, 519-24 [1990]) in 20 mM Tris•HCl pH 7.6, 3 mM manganese dichloride ($MnCl_2$), 3 mM magnesium chloride ($MgCl_2$), 1mM dithiothreitol and 3 µg/µl poly(Glu,Tyr) 4:1 (Sigma, Buchs, Switzerland), 8 µM [^{33}P]-ATP (0.2 µCi) , 1% dimethyl sulfoxide, and 0 to 100 µM of the compound to be tested are incubated together for 10 minutes at room temperature. The reaction is then terminated by the addition of 10 µl 0.25 M ethylenediaminetetraacetate (EDTA) pH 7. Using a multichannel dispenser (LAB SYSTEMS, USA), an aliquot of 20 µl is applied to a PVDF (= polyvinyl difluoride) Immobilon P membrane (Millipore, USA), through a Millipore microtiter filter manifold and connected to a vacuum. Following complete elimination of the liquid, the membrane is washed 4 times successively in a bath containing 0.5% phosphoric acid (H_3PO_4) and once with ethanol, incubated for 10 minutes each time while shaking, then mounted in a Hewlett Packard TopCount Manifold and the radioactivity measured after the addition of 10 µl Microscint® (ß-scintillation counter liquid). IC_{50}-values are determined by linear regression analysis of the percentages for the inhibition of each compound in three concentrations (as a rule 0.01, 0.1, and 1 µmol). The IC_{50}-values that can be found with compounds of formula I are in the range of 0.01 to 100 µM, preferably in the range from 0.01 to 50 µM.

The antitumor efficacy of the compounds of the invention can be demonstrated *in vivo* as follows:

In vivo activity in the nude mouse xenotransplant model: female BALB/c nude mice (8–12 weeks old), Novartis Animal Farm, Sisseln, Switzerland) are kept under sterile conditions with water and feed *ad libitum*. Tumors are induced either by subcutaneous injection of tumor cells into mice (for example, Du 145 prostate carcinoma cell line (ATCC No. HTB 81; see Cancer Research 37, 4049-58 (1978)) or by implanting tumor fragments (about 25 mg)

subcutaneously into the left flank of mice using a 13-gauge trocar needle under Forene® anaesthesia (Abbott, Switzerland). Treatment with the test compound is started as soon as the tumor has reached a mean volume of 100 mm^3. Tumor growth is measured two to three times a week and 24 hours after the last treatment by determining the length of two perpendicular axes. The tumor volumes are calculated in accordance with published methods (see Evans et al., Brit. J. Cancer 45, 466-8 [1982]). The antitumor efficacy is determined as the mean increase in tumor volume of the treated animals divided by the mean increase in tumor volume of the untreated animals (controls) and, after multiplication by 100, is expressed as T/C%. Tumor regression (given in %) is reported as the smallest mean tumor volume in relation to the mean tumor volume at the start of treatment. The test compound is administered daily by gavage.

A compound of formula I inhibits to varying degrees also other tyrosine kinases involved in signal transduction which are mediated by trophic factors, for example Abl kinase, kinases from the Src family, especially c-Src kinase, Lck, and Fyn; also kinases of the EGF family, for example, c-erbB2 kinase (HER-2), c-erbB3 kinase, c-erbB4 kinase; insulin-like growth factor receptor kinase (IGF-1 kinase), especially members of the PDGF-receptor tyrosine kinase family, such as PDGF-receptor kinase, CSF-1-receptor kinase, Kit-receptor kinase and VEGF-receptor kinase; and also serine/threonine kinases, all of which play a role in growth regulation and transformation in mammalian cells, including human cells.

The inhibition of c-erbB2 tyrosine kinase (HER-2) can be measured, for example, in the same way as the inhibition of EGF-R protein kinase (see House et al., Europ. J. Biochem. 140, 363-7 [1984]). The erbB2 kinase can be isolated, and its activity determined, using methods known *per se* (see T. Akiyama et al., Science 232, 1644 [1986]).

On the basis of these studies, a compound of formula I according to the invention shows therapeutic efficacy especially against disorders dependent on protein kinase, especially proliferative diseases.

On the basis of their efficacy as inhibitors of VEGF-receptor tyrosine kinase activity, compounds of the invention primarily inhibit the growth of vessels and are thus, for example, effective against a number of diseases associated with deregulated angiogenesis, especially retinopathies, psoriasis, haemangioblastoma, haemangioma, and especially neoplastic dis-

eases (solid tumors), such as especially breast cancer, cancer of the colon, lung cancer (especially small-cell lung cancer), or cancer of the prostate. A compound of formula I inhibits the growth of tumors and is especially suited also to preventing the metastatic spread of tumors and the growth of micrometastases.

A compound of formula I can be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. A compound of formula I can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

Therapeutic agents for possible combination are especially one or more cytostatic or cytotoxic compounds, for example a chemotherapeutic agent or several selected from the group comprising an inhibitor of polyamine biosynthesis, an inhibitor of protein kinase, especially of serine/threonine protein kinase, such as protein kinase C, or of tyrosine protein kinase, such as epidermal growth factor receptor tyrosine kinase, a cytokine, a negative growth regulator, such as TGF-ß or IFN-ß, an aromatase inhibitor, a classical cytostatic, and an inhibitor of the interaction of an SH2 domain with a phosphorylated protein.

A compound according to the invention is not only for the (prophylactic and preferably therapeutic) management of humans, but also for the treatment of other warm-blooded animals, for example of commercially useful animals, for example rodents, such as mice, rabbits or rats, or guinea-pigs. Such a compound may also be used as a reference standard in the test systems described above to permit a comparison with other compounds.

In general, the invention relates also to the use of a compound of formula I for the inhibition of VEGF-receptor tyrosine activity, either in vitro or in vivo.

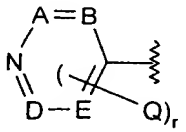
A compound of formula I may also be used for diagnostic purposes, for example with tumors that have been obtained from warm-blooded animal "hosts", especially humans, and implanted into mice to test them for decreases in growth after treatment with such a compound, in order to investigate their sensitivity to the said compound and thus to improve the detection and determination of possible therapeutic methods for neoplastic diseases in the original host.

With the groups of preferred compounds of formula I mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, for example, to replace more general definitions with more specific definitions or especially with definitions characterized as being preferred;

Preference is given to a compound of formula I wherein
wherein
W is O or S, preferably O;
X is NR_8
Y is CHR_9-$(CH_2)_n$ wherein
R_9 is H or lower alkyl, especially H or methyl, and
n is 0 to 3, preferably 0;
or Y is C=O or SO_2;
R_1 is phenyl that is unsubsituted or substituted by up to three, preferably 1 or two, substituents, especially selected from amino; mono- or disubstituted amino wherein the substituents are selected independently from lower alkyl, hydroxy-lower alkyl, phenyl-lower alkyl, lower alkanoyl, benzoyl and substituted benzoyl wherein the phenyl radical is substituted by one or two substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower-alkoxycarbonyl, lower alkanoyl and carbamoyl, and phenyl-lower alkoxycarbonyl wherein the phenyl radical radical is substituted by one or two substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower-alkoxycarbonyl, lower alkanoyl and carbamoyl; lower alkyl; substituted lower alkyl where especially up to three substituents may be present independently selected from the group containing halogen; especially fluorine, amino, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl; hydroxy, lower alkoxy; phenyl-lower alkoxy; phenyloxy; halogen-lower alkoxy, lower alkanoyloxy; benzoyloxy; lower alkoxycar-

bonyloxy; phenyl-lower alkoxycarbonyloxy; nitro; cyano; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; phenyloxycarbonyl; lower alkylcarbonyl; carbamoyl; N-mono- or N,N-disubstituted carbamoyl that is substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl, and hydroxy-lower alkyl, at the terminal nitrogen atom; amidino; guanidino; mercapto; sulfo; lower alkylthio; phenylthio; phenyl-lower alkylthio; lower alkylphenylthio; lower alkylsulfinyl; phenylsulfinyl; phenyl-lower alkylsulfinyl; lower alkylphenylsulfinyl; lower alkanesulfonyl; phenylsulfonyl; phenyl-lower alkylsulfonyl; lower alkylphenylsulfonyl; lower alkenyl; lower alkanoyl; halogen-lower alkylmercapto; halogen-lower alkylsulfonyl; dihydroxybora (-$B(OH)_2$); and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy; preferably phenyl which is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; lower alkyl, especially methyl or also ethyl or propyl; halogen-lower alkyl, especially trifluoromethyl; lower alkylsulfinyl, such as methylsulfinyl, and lower alkanesulfonyl, such as methane sulfonyl; most preferably R_1 is 3- or 4-chlorophenyl, 3-bromophenyl, 3- or 4-methylphenyl, 3- or 4-tert-butylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 4-chloro-3-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 4-methylsulfinylphenyl, 4-methanesulfonylphenyl or 2,1,3-benzodiazolyl;

R_2 is imidazolyl, especially imidazol-4-yl, quinolyl, especially 4-quinolyl, or more preferably a moiety of the formula Ib



(Ib)

wherein

r is 0 to 2, especially 0 or 1;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N; preferably, each of A, B, D and E is CH; and

Q is lower alkyl, especially methyl; most preferably R_2 is 4-pyridyl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or lower alkyl; and

R_7 and R_8, independently of each other, are H or lower alkyl, especially H or methyl;

or a salt thereof.

Special preference is given to a compound of formula I, especially formula IA, wherein
W is O;
X is NR_8
Y is CHR_9-$(CH_2)_n$ wherein
R_9 is H or methyl, and
n is 0;
or Y is C=O or SO_2;
R_1 is phenyl which is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; lower alkyl, especially methyl or also ethyl or propyl; halogen-lower alkyl, especially trifluoromethyl; lower alkylsulfinyl, such as methylsulfinyl, and lower alkanesulfonyl, such as methane sulfonyl; most preferably R_1 is 3- or 4-chlorophenyl, 3-bromophenyl, 3- or 4-methylphenyl, 3- or 4-tert-butylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 4-chloro-3-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 4-methylsulfinylphenyl, 4-methanesulfonylphenyl or 2,1,3-benzodiazolyl;

R_2 is imidazolyl, especially imidazol-4-yl, quinolyl, especially 4-quinolyl, 2-methyl-pyridin-4-yl or more preferably 4-pyridyl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or methyl; and
R_7 and R_8, independently of each other, are H or methyl;

or a salt thereof.

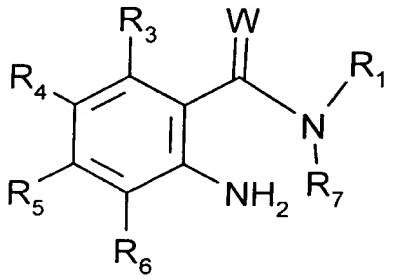
More special preference is given to a compound of formula I such as is mentioned in the Examples below, or a pharmaceutically acceptable salt thereof, especially a compound of the formula I or a salt thereof specifically mentioned in the Examples.

High preference is given to a compound selected from
2-[(4-pyridyl)methyl]amino-N-(4-trifluoromethylphenyl)benzamide;
2-[(4-pyridyl)methyl]amino-N-(4-chlorophenyl)benzamide;
2-[(4-pyridyl)methyl]amino-N-(4-methylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(3-fluoro-4-methylphenyl)benzamide;
2-[(4-pyridyl)methyl]amino-N-(4-chloro-3-trifluoromethylphenyl)benzamide;
2-[(4-pyridyl)methyl]amino-N-(3-chloro-5-trifluoromethylphenyl)benzamide;
2-[(4-pyridyl)methyl]amino-N-(4-methylphenyl)-6-methylbenzamide; and
2-[(4-quinolyl)methyl]amino-N-(4-chloromethylphenyl)benzamide;
or a pharmaceutically acceptable salt thereof.

A compound of the invention may be prepared by processes that, though not applied hitherto for the new compounds of the present invention, are known *per se*, especially a process characterized in that

a) for the synthesis of a compound of the formula I wherein X represents NR_8, where R_8 is hydrogen and Y represents CHR_9-$(CH_2)_n$, each as indicated for a compound of formula I, and the remaining symbols A, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for a compound of the formula I, an aniline derivative of the formula II



(II)

wherein W, R_1, R_3, R_4, R_5, R_6 and R_7 are as defined for a compound of the formula I, is reacted with a carbonyl compound of the formula III

$$R_2\text{-}(CH_2)_n\text{-}\ C(R_9)=O \qquad \text{(III)}$$

wherein n, R_2 and R_9 are as defined for a compound of the formula I in the presence of a reducing agent; or

b) for the synthesis of a compound of the formula I wherein X is C(=O) or SO_2 and the remaining symbols R_1, R_2, R_3, R_4, R_5, R_6, R_7, W and X are as defined for a compound of the formula I, an aniline derivative of the formula II as defined under process variante a) is reacted with an acid of the formula IV

R_2-X-OH (IV)

or a reactive derivative thereof;

where the starting compounds defined in a) or b) may also be present with functional groups in protected form if necessary and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible;

any protecting groups in a protected derivative of a compound of the formula I are removed;

and, if so desired, an obtainable compound of formula I is converted into another compound of formula I, a free compound of formula I is converted into a salt, an obtainable salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.

Detailed description of the process variants:
In the more detailed description of the process below, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X, Y and W are as defined for compounds of formula 1, unless otherwise indicated.

Process a) (reductive alkylation)
The carbonyl compound of the formula III may also be present in the form of reactive derivative; however, the free aldehyde or ketone is preferred.

Reactive derivatives of the compounds of formula III are, for example, corresponding bisulfite adducts or especially semiacetals, acetals, semiketals or ketals of compounds of formula III with alcohols, for example lower alkanols; or thioacetals or thioketals of compounds of formula III with mercaptans, for example lower alkanesulfides.

The reductive alkylation is preferably carried out with hydrogenation in the presence of a catalyst, especially a noble metal catalyst, such as platinum or especially palladium, which is preferably bonded to a carrier material, such as carbon, or a heavy metal catalyst, such as Raney nickel, at normal pressure or at pressures of from 0.1 to 10 MegaPascal (MPa), or with reduction by means of complex hydrides, such as borohydrides, especially alkali metal cyanoborohydrides, for example sodium cyanoborohydride, in the presence of a suitable

acid, preferably relatively weak acids, such as lower alkanecarboxylic acids, especially acetic acid, or a sulfonic acid, such as p-toluenesulfonic acid; in customary solvents, for example alcohols, such as methanol or ethanol, or ethers, for example cyclic ethers, such as tetrahydrofuran, in the presence or absence of water.

Process b) (condensation)

The compounds of formula IV either contain a free carboxy or sulfo group or are in the form of a reactive derivative thereof, for example in the form of a derived activated ester or reactive anhydride, or in the form of a reactive cyclic amide. The reactive acid derivatives may also be formed *in situ*.

Activated esters of compounds of formula IV having a terminal carboxy group are especially esters unsaturated at the carbon atom linking the radical to be esterified, for example esters of the vinyl ester type, such as vinyl esters (obtainable, for example, by transesterification of a corresponding ester with vinyl acetate; activated vinyl ester method), carbamoyl esters (obtainable, for example, by treatment of the corresponding acid with an isoxazolium reagent; 1,2-oxazolium or Woodward method), or 1-lower alkoxyvinyl esters (obtainable, for example, by treatment of the corresponding acid with a lower alkoxyacetylene; ethoxyacetylene method), or esters of the amidino type, such as N,N'-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with a suitable N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide or especially N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide; carbodiimide method), or N,N-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with an N,N-disubstituted cyanamide; cyanamide method), suitable aryl esters, especially phenyl esters suitably substituted by electron-attracting substituents (obtainable, for example, by treatment of the corresponding acid with a suitably substituted phenol, for example 4-nitrophenol, 4-methylsulfonylphenol, 2,4,5-trichlorophenol, 2,3,4,5,6-pentachlorophenol or 4-phenyldiazophenol, in the presence of a condensation agent, such as N,N'-dicyclohexylcarbodiimide; activated aryl esters method), cyanomethyl esters (obtainable, for example, by treatment of the corresponding acid with chloroacetonitrile in the presence of a base; cyanomethyl esters method), thio esters, especially unsubstituted or substituted, for example nitro-substituted, phenylthio esters (obtainable, for example, by treatment of the corresponding acid with unsubstituted or substituted, for example nitro-substituted, thiophenols, *inter alia* by the anhydride or carbodiimide method; activated thiol esters method), or especially amino or

amido esters (obtainable, for example, by treatment of the corresponding acid with an N-hydroxyamino or N-hydroxyamido compound, for example N-hydroxysuccinimide, N-hydroxypiperidine, N-hydroxyphthalimide, N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide, 1-hydroxybenzotriazole or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one, for example by the anhydride or carbodiimide method; activated N-hydroxy esters method). Internal esters, for example γ-lactones, can also be used.

Anhydrides of acids may be symmetric or preferably mixed anhydrides of those acids, for example anhydrides with inorganic acids, such as acid halides, especially acid chlorides (obtainable, for example, by treatment of the corresponding acid with thionyl chloride, phosphorus pentachloride, phosgene or oxalyl chloride; acid chloride method), azides (obtainable, for example, from a corresponding acid ester *via* the corresponding hydrazide and treatment thereof with nitrous acid; azide method), anhydrides with carbonic acid semi-esters, for example carbonic acid lower alkyl semiesters (especially chloroformic acid methyl esters) (obtainable, for example, by treatment of the corresponding acid with chloroformic acid lower alkyl esters or with a 1-lower alkoxycarbonyl-2-lower alkoxy-1,2-dihydroquinoline; mixed O-alkylcarbonic acid anhydrides method), or anhydrides with dihalogenated, especially dichlorinated, phosphoric acid (obtainable, for example, by treatment of the corresponding acid with phosphorus oxychloride; phosphorus oxychloride method), anhydrides with other phosphoric acid derivatives (for example those obtainable with phenyl-N-phenylphosphoramidochloridate or by reaction of alkylphosphoric acid amides in the presence of sulfonic acid anhydrides and/or racemisation-reducing additives, such as N-hydroxybenzotriazole, or in the presence of cyanophosphonic acid diethyl ester) or with phosphorous acid derivatives, or anhydrides with organic acids, such as mixed anhydrides with organic carboxylic acids (obtainable, for example, by treatment of the corresponding acid with an unsubstituted or substituted lower alkane- or phenyl-lower alkane-carboxylic acid halide, for example phenylacetic acid chloride, pivalic acid chloride or trifluoroacetic acid chloride; mixed carboxylic acid anhydrides method) or with organic sulfonic acids (obtainable, for example, by treatment of a salt, such as an alkali metal salt, of the corresponding acid with a suitable organic sulfonic acid halide, such as a lower alkane- or aryl-, for example methane- or p-toluene-sulfonic acid chloride; mixed sulfonic acid anhydrides method) and symmetric anhydrides (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or 1-diethylaminopropyne; symmetric anhydrides method).

Suitable cyclic amides are especially amides with five-membered diazacycles of aromatic character, such as amides with imidazoles, for example imidazole (obtainable, for example, by treatment of the corresponding acid with N,N'-carbonyldiimidazole; imidazole method), or pyrazole, for example 3,5-dimethylpyrazole (obtainable, for example, *via* the acid hydrazide by treatment with acetylacetone; pyrazolide method).

As mentioned, derivatives of carboxylic acids used as acylating agents may also be formed *in situ*. For example, N,N'-disubstituted amidino esters may be formed *in situ* by reacting a mixture of the starting material of formula II and the acid used as acylating agent in the presence of a suitable N,N'-disubstituted carbodiimide, for example N,N'-cyclohexylcarbodiimide or especially N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide. In addition, amino or amido esters of the acids used as acylating agents may be formed in the presence of the starting material of formula II to be acylated, by reacting a mixture of the corresponding acid and amino starting materials in the presence of an N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide, and of an N-hydroxyamine or N-hydroxyamide, for example N-hydroxysuccinimide, where appropriate in the presence of a suitable base, for example 4-dimethylamino-pyridine. Furthermore, activation *in situ* can be achieved by reaction with N,N,N',N'-tetraalkyluronium compounds, such as O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (in the presence or absence of 1,8-diazabicyclo[5.4.0]-undec-7-ene(1,5-5)) or O-(3,4-dihydro-4-oxo-1,2,3-benzotriazolin-3-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate. Finally, phosphoric acid anhydrides of the carboxylic acids of formula IV can be prepared *in situ* by reacting an alkylphosphoric acid amide, such as hexamethylphosphoric acid triamide, in the presence of a sulfonic acid anhydride, such as 4-toluenesulfonic acid anhydride, with a salt, such as a tetrafluoroborate, for example sodium tetrafluoroborate, or with another derivative of hexamethylphosphoric acid triamide, such as benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluoride, preferably in the presence of a racemisation-reducing additive, such as N-hydroxybenzotriazole.

The amino group of compounds of formula II that participates in the reaction preferably is in free form, especially when the carboxy or sulfonyl group reacting therewith is present in reactive form; it may, however, itself have been derivatised, for example by reaction with a phosphite, such as diethylchlorophosphite, 1,2-phenylene chlorophosphite, ethyldichlorophosphite, ethylene chlorophosphite or tetraethylpyrophosphite. A derivative of such a

compound having an amino group is, for example, also a carbamic acid halide or an isocyanate, the amino group that participates in the reaction being substituted by halocarbonyl, for example chlorocarbonyl, or modified in the form of an isocyanate group, respectively.

Condensation to form an amide bond can be carried out in a manner known *per se*, for example as described in standard works, such as Houben-Weyl, "Methoden der organischen Chemie", 4th edition, Volume 15/II (1974), Volume IX (1955), Volume E11 (1985), Georg Thieme Verlag, Stuttgart, "The Peptides" (E. Gross and J. Meienhofer, eds.), Volumes 1 and 2, Academic Press, London and New York, 1979/1980, or M.Bodansky, "Principles of Peptide Synthesis", Springer-Verlag, Berlin 1984.

If desired, an organic base is added, preferably a tertiary amine, for example a tri-lower alkylamine, especially ethyldiisopropylamine or more especially triethylamine, and/or a heterocyclic base, for example 4-dimethylaminopyridine or preferably N-methylmorpholine or pyridine.

The condensation of activated esters, reactive anhydrides or reactive cyclic amides with the corresponding amines is customarily carried out in the presence of an anorganic base, such as an alkaline metal hydrogencarbonate of carbonate, or especially an organic base, for example simple tri-lower alkylamines, for example triethylamine or tributylamine, or one of the above-mentioned organic bases. If desired, a condensation agent is additionally used, for example as described for free carboxylic acids.

The condensation of acid anhydrides with amines can be effected, for example, in the presence of inorganic carbonates, for example ammonium or alkali metal carbonates or hydrogen carbonates, such as sodium or potassium carbonate or hydrogen carbonate (if desired together with a sulfate).

Carboxylic acid chlorides, for example the chlorocarbonic acid derivatives derived from the acid of formula IV, are condensed with the corresponding amines preferably in the presence of an organic amine, for example the above-mentioned tri-lower alkylamines or heterocyclic bases, where appropriate in the presence of a hydrogen sulfate or a hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide.

The condensation is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran or dioxane, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in a mixture thereof, as appropriate at reduced or elevated temperature, for example in a temperature range of from approximately -40° to approximately +100°C, preferably from approximately -10° to approximately +70°C, and when arylsulfonyl esters are used also at approximately from +100° to +200°C, especially at temperatures of from 10° to 30°C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

Aqueous, for example alcoholic, solvents, for example ethanol, or aromatic solvents, for example benzene or toluene, may also be used. When alkali metal hydroxides are present as bases, acetone may also be added where appropriate.

All remarks made above with regard to the carbonic acids of the formula IV apply, mutatis mutandis, to the respective sulfonic acids, as appropriate.

Protecting groups

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a compound of formulae II , III and/or IV, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products.The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

Additional process steps

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formula I) may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 130 to 170°C, one molecule of the acid being expelled per molecule of a compound of formula I.

Salts can usually be converted to free compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corres-

ponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

A compound of formula I, wherein W is O, can be converted into the respective compound wherein W is S, for example, by using an appropriate sulfur compound, e.g. using reaction with Lawesson's reagent (2,4-bis-(4-methoxyphenyl)2,4-dithioxo-1,2,3,4-dithiaphosphetan) in a halogenated carbon hydrate, such as dichloromethane, or an aprotic solvent, such as toluene or xylene, at temperatures from about 30 °C to reflux.

A compound of the formula I wherein any one or both of R_7 and R_9 is hydrogen and is part of an amide (Y in formula I is C(=O) or sulfonamide (Y is SO_2) bond can be converted to the respective compound wherein R_7 and/or R_9 is lower alkyl by reaction e.g. with a diazo lower alkyl compound, especially diazomethane, in an inert solvent, preferably in the presence of a noble metal catalyst, especially in dispersed form, e.g. copper, or a noble metal salt, e.g. cupper(I)-chloride or copper(II)-sulfate. Also reaction with lower alkylhalogenides is possible, or with other leaving group carrying lower alkanes, e.g. lower alkyl alcohols esterified by a strong organic sulfonic acid, such as a lower alkane sulfonic acid (optionally substituted by halogen, such as fluoro), an aromatic sulfonic acid, for example unsubstituted or substituted benzene-sulfonic acid, the substituents preferably being selected from lower alkyl, such as methyl, halogen, such as bromo, and/or nitro, e.g. esterified by methane sulfonic acid, trimethane sulfonic acid or p-toluol sulfonic acid.

Also, in a compound of the formula I wherein R_8 is hydrogen and Y is CHR_9-$(CH_2)_n$, the alkylation may be made with such alkylating agents.

In both cases, the alkylation takes place especially in aqueous solution and/or in the presence of polar solvents, typically alcohols, for example methanol, ethanol, isopropanol, or ethylene glycol, ethers, typically dioxane, amides, typically dimethylformamide, or phenols,

typically phenol, and also under non-aqueous conditions, in non-polar solvents, typically benzene and toluene, or in benzene/water emulsions, where applicable in the presence of acidic or basic catalysts, for example leaches, typically sodium hydroxide solution, or in the presence of solid-phase catalysts, typically aluminium oxide, that have been doped with hydrazine, in ethers, for example diethylether, generally at temperatures from about 0°C to the boiling temperature of the corresponding reaction mixture, preferably between 20°C and reflux temperature, if necessary under increased pressure, e.g. in a sealed tube, a temperature in excess of boiling point also being possible, and/or under inert gas, typically nitrogen or argon.

It should be amphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates.

General process conditions

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralisiing agents, for example ion exchangers, typically cation exchangers, for example in the H^+ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at -80 to -60°C, at room temperature, at - 20 to 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

At all reaction stages, isomeric mixtures that occur can be separated into their individual isomers, e.g. diastereomers or enantiomers, or into any mixtures of isomers, e.g. racemates or diastereomeric mixtures, typically as described under "Additional process steps".

In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective reactions, allowing for example easier recovery of individual isomers.

The solvents from which those can be selected which are suitable for the reaction in question include for example water, esters, typically lower alkyl-lower alkanoates, e.g diethyl acetate, ethers, typically aliphatic ethers, e.g. diethylether, or cyclic ethers, e.g. tetrahydrofuran, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically methanol, ethanol or 1- or 2-propanol, nitriles, typically acetonitrile, halogenated hydrocarbons, typically dichloromethane, acid amides, typically dimethylformamide, bases, typically heterocyclic nitrogen bases, e.g. pyridine, carboxylic acids, typically lower alkanecarboxylic acids, e.g. acetic acid, carboxylic acid anhydrides, typically lower alkane acid anhydrides, e.g. acetic anhydride, cyclic, linear, or branched hydrocarbons, typically cyclohexane, hexane, or isopentane, or mixtures of these solvents, e.g. aqueous solutions, unless otherwise stated in the description of the process. Such solvent mixtures may also be used in processing, for example through chromatography or distribution.

The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound *in situ*. In the preferred embodiment, one starts from those starting materials which lead to the compounds described hereinabove as preferred, particularly as especially preferred, primarily preferred, and/or preferred above all.

In the preferred embodiment, a compound of formula I is prepared according to or in analogy to the processes and process steps defined in the Examples.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

Pharmaceutical preparations, methods, and uses

The present invention relates also to pharmaceutical compositions that comprise a compound of formula I as active ingredient and that can be used especially in the treatment of the diseases mentioned at the beginning. Compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous, intramuscular or subcutaneous administration, to warm-blooded animals, especially humans, are especially preferred. The compositions comprise the active ingredient alone or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration.

The invention relates also to pharmaceutical compositions for use in a method for the prophylactic or especially therapeutic management of the human or animal body, to a process for the preparation thereof (especially in the form of compositions for the treatment of tumors) and to a method of treating tumor diseases, especially those mentioned hereinabove.

The invention relates also to processes and to the use of compounds of formula I for the preparation of pharmaceutical preparations which comprise compounds of formula I as active component (active ingredient).

In the preferred embodiment, a pharmaceutical preparation is suitable for administration to a warm-blooded animal, especially humans or commercially useful mammals suffering from a disease responsive to an inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, for example psoriasis or especially a neoplastic disease, and comprises an effective quantity of a compound of formula I for the inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, or a pharmaceutically acceptable salt thereof, if salt-forming groups are present, together with at least one pharmaceutically acceptable carrier.

A pharmaceutical composition for the prophylactic or especially therapeutic management of neoplastic and other proliferative diseases of a warm-blooded animal, especially a human or a commercially useful mammal requiring such treatment, especially suffering from such a disease, comprising as active ingredient in a quantity that is prophylactically or especially therapeutically active against the said diseases a novel compound of formula I, is likewise preferred.

The pharmaceutical compositions comprise from approximately 1% to approximately 95% active ingredient, single-dose administration forms comprising in the preferred embodiment from approximately 20% to approximately 90% active ingredient and forms that are not of single-dose type comprising in the preferred embodiment from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories, or capsules. Further dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lip-sticks, drops, sprays, dispersions, etc. Examples are capsules containing from about 0.05 g to about 1.0 g active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® [polyoxyethylene(20)sorbitan mono-oleate; trademark of ICI Americas, Inc, USA].

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these

fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate from Gattefossé, Paris), "Labrafil M 1944 CS" (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyr-

rolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The invention relates likewise to a process or a method for the treatment of one of the pathological conditions mentioned hereinabove, especially a disease which responds to an inhibition of the VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, especially a corresponding neoplastic disease or also psoriasis. The compounds of formula I can be administered as such or especially in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment. In the case of an individual having a bodyweight of about 70 kg the daily dose administered is from approximately 0.1 g to approximately 5 g, preferably from approximately 0.5 g to approximately 2 g, of a compound of the present invention.

The present invention relates especially also to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, especially a compound of formula I which is said to be preferred, or a pharmaceutically acceptable salt thereof, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, especially a neoplastic disease or also psoriasis, more especially if the disease responds to an inhibition of angiogenesis or an inhibition of VEGF-receptor tyrosine kinase.

The present invention relates especially also to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, especially a compound of formula I which is said to be preferred, or a pharmaceutically acceptable salt thereof, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, preferably a disease which responds to an inhibition of VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, especially a neoplastic disease or also psoriasis, more especially if the said disease responds to an inhibition of VEGF-receptor tyrosine kinase or angiogenesis.

The present invention relates especially also to the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, especially a compound of formula I which is said to be preferred, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical formulation for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, especially a neoplastic disease or also

psoriasis, more especially if the disease responds to an inhibition of VEGF-receptor tyrosine kinase or angiogenesis.

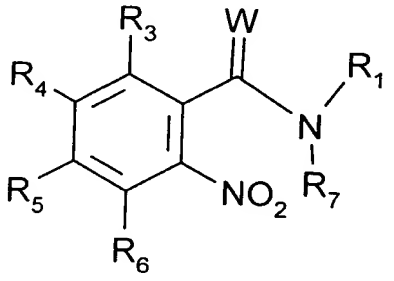
The preferred dose quantity, composition, and preparation of pharmaceutical formulations (medicines) which are to be used in each case are described above.

Starting materials

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of the formula II, III and IV are known, are commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

For example, an aniline of the formula II can be prepared from a nitro compound of the formula V,

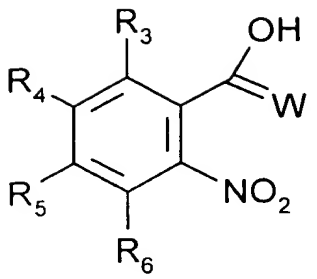


(V)

wherein R_1, R_3 to R_7 and W have the meanings as given under formula I.

The reduction preferably takes place in the presence of a suitable reducing agent, such as tin(II) chloride or hydrogen in the presence of an appropriate catalyst, such as Raney nickel (then preferably the hydrogen is used under pressure, e.g. between 2 and 20 bar) or PtO_2, in an appropriate solvent, e.g. an alcohol, such as methanol. The reaction temperature is preferably between 0 and 80 °C, especially 15 to 30 °C.

A nitro compound of the formula V is accessible by reaction of an acid of the formula VI,



(VI)

wherein W is oxygen and R_3 to R_6 are as defined above, or an activated derivative thereof, is reacted with an amine of the formula VII,

$$HNR_1R_7 \qquad (VII)$$

wherein R_1 and R_7 are as defined under formula I. The reactive derivatives and reaction conditions are analogous to those for reaction of a compound of the formula II and of the formula IV given under process variante b), if instead of the aniline of the formula II the amine of the formula VII is used and instead of the acid of the formula IV that of formula VI.

If required, W = O can be changed to W = S with Lawesson's agent, as described above for the analogous conversion of a compound of formula I with W = O into one with W = S.

It would also be possible to first reduce the nitro compound of the formula VI to the corresponding aniline compound under reaction conditions analogous to those for the reduction of nitro compounds of the formula V and then react the resulting anilino compound with the amino compound of formula VII under analogous conditions as decribed above. However, it may then be nesessary to protect the aniline amino group.

All remaining starting materials of are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described in the Examples.

In the preparation of starting materials, existing functional groups which do not participate in the reaction should, if necessary, be protected. Preferred protecting groups, their introduction and their removal are described under "protecting goups" or in the Examples.

Examples:

The following Examples serve to illustrate the invention without limiting the invention in its scope.

Temperatures are measured in degrees celsius (°C). Unless otherwise indicated, the reactions take place at room temperature.

A) Preparation of Intermediates:

1. Intermediate 1a: 2-Nitro-*N*-(4-trifluoromethylphenyl)benzamide

A solution containing 2-nitrobenzoyl chloride (Fluka, Buchs, Switzerland) (1.97 mL, 15 mmol) and 4-dimethylaminopyridine (Fluka, Buchs, Switzerland) (10 mg) in dichloromethane (10 mL) is added to a stirred mixture of 4-aminobenzotrifluoride (Fluka, Buchs, Switzerland) (2.66 g, 16.5 mmol) and triethylamine (1.90 g, 18.8 mmol) in dichloromethane (100 mL) 25°C under an argon atmosphere and the mixture is stirred for 16 hours at 25°C. The stirred mixture is then treated with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and then extracted with dichoromethane (2 x 50 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 10 - 50% ethyl acetate in hexane, to give the title compound as a colourless crystalline solid.

The following compounds are prepared analogously by utilising the appropriate amine (the supplier of which is mentioned in each case in parenthesis):

(1b) 2-Nitro-*N*-(4-chlorophenyl)benzamide. (Fluka, Buchs, Switzerland)

(1c) 2-Nitro-*N*-(4-methylphenyl)benzamide. (Fluka, Buchs, Switzerland)

(1d) 2-Nitro-*N*-(3-fluoro-4-methylphenyl)benzamide. (Aldrich, Buchs, Switzerland)

(1e) 2-Nitro-*N*-(4-chloro-3-trifluoromethylphenyl)benzamide. (Aldrich, Buchs, Switzerland)

(1f) 2-Nitro-*N*-(3-chloro-5-trifluoromethylphenyl)benzamide (utilizing 3-amino-5-chlorobenzotrifluoride, prepared from 4-amino-3-chloro-5-nitrobenzotrifluoride (Maybridge Chemical Co. Ltd.) as described in European Patent Application EP 0 516 297)

(1g) 2-Nitro-N-(3-trifluoromethylphenyl)benzamide. (Fluka, Buchs, Switzerland)

2. Intermediate 2a: 2-Amino-*N*-(4-trifluoromethylphenyl)benzamide

A solution of 2-nitro-*N*-(4-trifluoromethylphenyl)benzamide (1a) (1.92 g, 6.19 mmol) in methanol (200 mL) is hydrogenated at 5 bar over Raney nickel (400 mg) at 21°C. The calculated

amount of hydrogen is taken up in 1 hour. The mixture is then filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by recrystallisation from dichloromethane - hexane to give the title compound as a colourless crystalline solid, m.p. 160-161°C.

The following compounds are prepared analogously by utilising the appropriate amine:
(2b) 2-Amino-*N*-(4-chlorophenyl)benzamide, m.p. of the hydrochloride salt 156-173°C, utilising intermediate 1b.
(2c) 2-Amino-*N*-(4-methylphenyl)benzamide, utilising intermediate 1c.
(2d) 2-Amino-*N*-(3-fluoro-4-methylphenyl)benzamide, m.p. 149-151°C, utilising intermediate 1d.
(2e) 2-Amino-*N*-(4-chloro-3-trifluoromethylphenyl)benzamide, m.p. 148-150 °C, utilising intermediate 1e.
(2f) 2-Amino *N*-(3-chloro-5-trifluoromethylphenyl)benzamide, m.p. 174-175°C, utilising intermediate 1f.
(2g) 2-Amino-N-(3-trifluoromethylphenyl)benzamide, m.p. 131-133 °C, utilising intermediate 1g.

Intermediate 2h: 2-Amino *N*-(4-methylphenyl)benzamide

A solution of 4-*tert*-butylaniline (Aldrich; 9.00 g, 60.3 mmol) in dimethylformamide (20 mL) ia added to a stirred solution of isatoic anhydride (9.75 g, 60 mmol) in dimethylformamide (80 mL) at 100°C. The mixture is stirred at 100°C for 4 hours. The solvent is then evaporated off under reduced pressure to give a residue which is dissolved in ethyl acetate (300 mL) and washed with saturated aqueous ammonium chloride solution. The solution is dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the product which is purified by column chromatography on silica gel, eluent 10% ethyl acetate in hexane and recrystallised from *t*-butylmethyl ether-cyclohexane to give the title compound as a colourless crystalline solid, m.p. 132-134 °C.

Intermediate 2i: 2-Amino *N*-(4-methylphenyl)-6-methylbenzamide
(i) 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methylbenzoic acid
A stirred solution of 2-amino-6-methylbenzoic acid (Aldrich, Buchs, Switzerland) (9.90 g, 65.5 mmol), triethylamine (12.4 mL, 9.00 g, 89.10 mmol) in dry dimethylformamide (300 mL) under an argon atmosphere, is treated with di-*t*-butyl dicarbonate (19.44 g, 89.1 mmol) and stirred at 18°C for 18 hours. The solvent is evaporated off under reduced pressure to give a residue

which is treated with aqueous citric acid solution (100 mL of 10%) and extracted with dichloromethane (2 x 100 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the product which is purified by column chromatography on silica gel, eluent 5% methanol in dichloromethane and recrystallised from *t*-butylmethyl ether-hexane to give the title compound as a colourless crystalline solid.

(ii) *N*-(4-methylphenyl)-2-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methylbenzamide
Firstly *N*-methylmorpholine (6.15 mL, 5.64 g, 55.8 mmol) and then *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (10.15 g, 26.8 mmol) are added to a stirred mixture of 2-[[(1,1-dimethylethoxy)carbonyl]amino]-6-methylbenzoic acid (5.60 g, 22.3 mmol) and *p*-toluidine 4.78 g, 44.6 mmol) in dry dimethylformamide (110 mL) under an argon atmosphere, and stirred at 18°C for 16 hours. The solvent is evaporated off under reduced pressure to give a residue which is treated with aqueous sodium hydrogen carbonate solution (200 mL of 10%) and extracted with dichloromethane (3 x 100 mL). The combined extracts are washed with aqueous citric acid solution (100 mL of 10%), dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 20% ethyl acetate in hexane and recrystallised from *tert*-butylmethyl ether-hexane to give the title compound as a colourless crystalline solid, m.p. 250 °C.

(iii) 2-Amino *N*-(4-methylphenyl)-6-methylbenzamide, hydrochloride
A stirred solution of *N*-(4-methylphenyl)-2-[[(1,1-dimethylethoxy)carbonyl]amino]-6-methylbenzamide (1.67 g, 4.90 mmol) in methanol (4 mL) under an argon atmosphere, is treated with a saturated solution of hydrogen chloride in dioxane (30 mL) and stirred at 18°C for 210 minutes. The solvent is evaporated off under reduced pressure to give the crude product which is purified by recrystallisation from methanol - di-isopropyl ether to give the title compound as a colourless crystalline solid, m.p. 217-220 °C.

Example 1: 2-[(4-Pyridyl)methyl]amino-*N*-(4-trifluoromethylphenyl)benzamide
Sodium cyanoborohydride (0.80 g of 90%, 11.5 mmol) is added in portions over 30 minutes to a stirred mixture of acetic acid (0.15 mL), 4-pyridinecarboxaldehyde (Fluka, Buchs, Switzerland) (1.00 g, 3.57 mmol) and 2-amino-*N*-(4-trifluoromethylphenyl)benzamide (1.00 g, 3.57 mmol) in methanol (15 mL) at 25°C under an argon atmosphere. The mixture is stirred

for 16 hours, then diluted with dichloromethane (100 mL) and treated with a saturated aqueous solution of sodium hydrogen carbonate (50 mL). The mixture is stirred for an additional 5 min and then extracted with dichoromethane (3 x 50 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product that is purified by column chromatography on silica gel, eluent 33% ethyl acetate in hexane and recrystallised from 2-propanol - hexane to give the title compound as a colourless crystalline solid, m.p. 171-175°C and having the following physical characteristics: ^{1}H-NMR (DMSO-d_6) d 4.49 (d, J = 6.1 Hz, 2H), 6.56 (d, J = 8.4 Hz, 1H), 6.66 (t, J = 8.5 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 5.9 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.72 (m, 1H), 7.90 (t, J = 6.1 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 8.49 (d, J = 5.9 Hz, 2H) and 10.46 (s, 1H).

The following compounds are prepared analogously by utilising the appropriate amine:

Example 2: 2-[(4-Pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide, m.p. 134-139 °C, utilising intermediate 2b

Example 3: 2-[(4-Pyridyl)methyl]amino-*N*-(4-methylphenyl)benzamide, utilising intermediate 2c

Example 4: 2-[(4-Pyridyl)methyl]amino-*N*-(3-fluoro-4-methylphenyl)benzamide is prepared utilising intermediate 2d. Following purification by chromatography, the base is dissolved in ethyl acetate and treated with a solution of hydrogen chloride in dichloromethane. The precipitated product is filtered off and recrystallized from dichloromethane-hexane to afford the dihydrochloride salt, m.p. 116-124 °C.

Example 5: 2-[(4-Pyridyl)methyl]amino-*N*-(4-chloro-3-trifluoromethylphenyl)benzamide, m.p. 162-172°C, utilising intermediate 2e.

Example 6: 2-[(4-Pyridyl)methyl]amino-*N*-(3-chloro-5-trifluoromethylphenyl)benzamide, m.p. 190 - 194°C, utilising intermediate 2f.

Example 7: 2-[(4-Pyridyl)methyl]amino-N-(3-trifluoromethylphenyl)benzamide, utilising intermediate 2g.

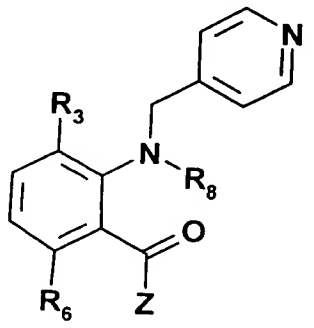
Example 8: 2-[(4-Pyridyl)methyl]amino-N-(4-tert-butylphenyl)benzamide, utilising intermediate 2h.

Example 9: 2-[(4-Pyridyl)methyl]amino-*N*-(4-methylphenyl)-6-methylbenzamide, m.p. 162-163 °C, utilising intermediate 2i.

Example 10: 2-[(4-Quinolinyl)methyl]amino-*N*-(4-chlorophenyl)benzamide, utilising intermediate 2b and 4-quinoline-carboxaldehyde (Fluka, Buchs, Switzerland).

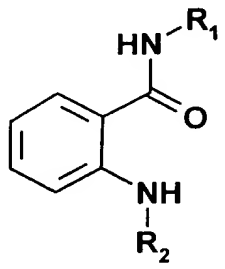
Example 11: *N*-[2-(Phenylaminocarbonyl)phenyl]-4-pyridinecarboxamide
Isonicotinoyl chloride hydrochloride (Lancaster Synthesis) (377 mg, 2.12 mmol) is added to a stirred mixture of 2-amino-*N*-(4-chlorophenyl)benzamide (500 mg, 1.77 mmol), triethylamine (0.988 mL, 7.08 mmol) and 4-dimethylaminopyridine (20 mg) in 1,2-dichloroethane (10 mL) at 20°C under an argon atmosphere. The mixture is stirred for 16 hours, then treated with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and extracted with dichoromethane (3 x 50 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by recrystallisation from dichloromethane – diisopropyl ether to give the title compound as a colourless crystalline solid, m.p. 231-237°C.

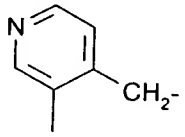
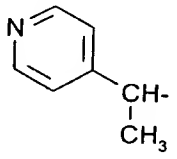
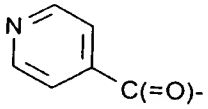
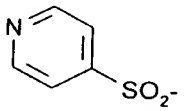
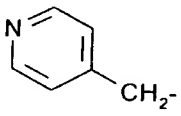
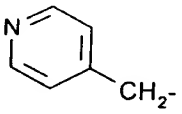
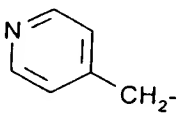
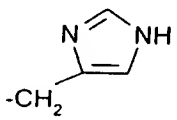
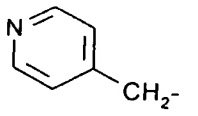
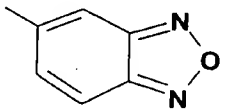
In analogy to the Examples given above, the following compounds falling under formula I are prepared:

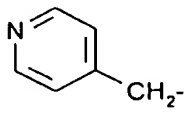
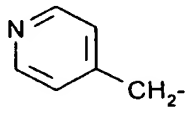
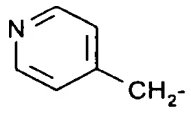
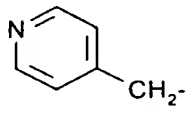


Example	R_8	Z	R_3	R_6
12	CH_3	HNC_6H_4Cl	H	H
13	CH_3	$HNC_6H_4CH_3$	H	H
14	H	HNC_6H_4Cl	CH_3	H
15	H	HNC_6H_4Cl	H	CH_3

In analogy to the Examples given above, the following compounds falling under formula I are prepared:



Example	R_2	R_1
16		4-ClC_6H_4
17		4-ClC_6H_4
18		4-ClC_6H_4
19		4-ClC_6H_4
20		4-$F_3CC_6H_4$
21		3-$CH_3SOC_6H_4$
22		3-$CH_3SO_2C_6H_4$
23		4-ClC_6H_4
24		

25		3-$CH_3C_6H_4$
26		3-$(CH_3)_3CC_6H_4$
27		3-ClC_6H_4
28		3-BrC_6H_4

Example 29: Test for activity against Flt-1 VEGF-receptor tyrosine kinase.

The test is conducted using Flt-1 VEGF-receptor tyrosine kinase, as described hereinabove. The IC_{50} values determined are given below, insofar as they have been accurately recorded:

Title compound from Example	IC_{50} (μM)
2	0.18
3	0.26
5	0.56
7	12

Example 30: Soft capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition

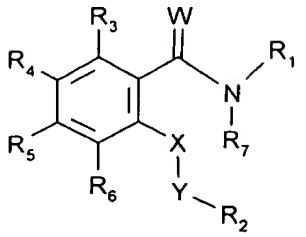
Active ingredient 250 g

Lauroglycol 2 litres

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 µm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

What is claimed is:

1. A compound of formula I,



(I)

wherein

W is O or S;

X is NR_8

Y is CHR_9-$(CH_2)_n$ wherein

R_9 is hydrogen or lower alkyl, and

n is an integer of from and including 0 to and including 3;

or Y is C=O or SO_2;

R_1 is aryl or heteroaryl

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms;

any of R_3 , R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or a salt thereof.

2. A compound of formula I according to claim 1,

wherein

W is O or S, preferably O;

X is NR_8

Y is CHR_9-$(CH_2)_n$ wherein

R_9 is H or lower alkyl, and

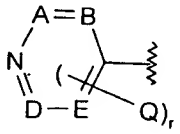
n is 0 to 3;

or Y is C=O or SO_2;

R_1 is phenyl that is unsubsituted or substituted by up to three substituents selected from amino; mono- or disubstituted amino wherein the substituents are selected independently from lower alkyl, hydroxy-lower alkyl, phenyl-lower alkyl, lower alkanoyl, benzoyl and substituted benzoyl wherein the phenyl radical is substituted by one or two substituents selected

from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower-alkoxycarbonyl, lower alkanoyl and carbamoyl, and phenyl-lower alkoxycarbonyl wherein the phenyl radical radical is substituted by one or two substituents selected from nitro, amino, halogen, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower-alkoxycarbonyl, lower alkanoyl and carbamoyl; lower alkyl; substituted lower alkyl where especially up to three substituents are present independently selected from the group containing halogen, N-lower alkylamino, N,N-di-lower alkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl and phenyl-lower alkoxycarbonyl; hydroxy, lower alkoxy; phenyl-lower alkoxy; phenyloxy; halogen-lower alkoxy, lower alkanoyloxy; benzoyloxy; lower alkoxycarbonyloxy; phenyl-lower alkoxycarbonyloxy; nitro; cyano; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; phenyloxycarbonyl; lower alkylcarbonyl; carbamoyl; N-mono- or N,N-disubstituted carbamoyl that is substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl and hydroxy-lower alkyl, at the terminal nitrogen atom; amidino; guanidino; mercapto; sulfo; lower alkylthio; phenylthio; phenyl-lower alkylthio; lower alkylphenylthio; lower alkylsulfinyl; phenylsulfinyl; phenyl-lower alkylsulfinyl; lower alkylphenylsulfinyl; lower alkanesulfonyl; phenylsulfonyl; phenyl-lower alkylsulfonyl; lower alkylphenylsulfonyl; lower alkenyl; lower alkanoyl; halogen-lower alkylmercapto; halogen-lower alkylsulfonyl; dihydroxybora ($-B(OH)_2$); and lower alkylene dioxy bound at adjacent C-atoms of the ring;

R_2 is imidazolyl, quinolyl or a moiety of the formula Ib



(Ib)

wherein

r is 0 to 2;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N; preferably; and

Q is lower alkyl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or lower alkyl; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or a salt thereof.

3. A compound of formula I according to claim 1, wherein

W is O;

X is NR_8

Y is CHR_9-$(CH_2)_n$ wherein

R_9 is H or methyl, and

n is 0;

or Y is C=O or SO_2;

R_1 is phenyl which is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen; lower alkyl; halogen-lower alkyl; lower alkylsulfinyl; and lower alkanesulfonyl;

R_2 is imidazolyl, quinolyl, 2-methyl-pyridin-4-yl or 4-pyridyl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or methyl; and

R_7 and R_8, independently of each other, are H or methyl;

or a salt thereof.

4. A compound of formula I according to claim 1 selected from

2-[(4-pyridyl)methyl]amino-N-(4-trifluoromethylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(4-chlorophenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(4-methylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(3-fluoro-4-methylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(4-chloro-3-trifluoromethylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(3-chloro-5-trifluoromethylphenyl)benzamide;

2-[(4-pyridyl)methyl]amino-N-(4-methylphenyl)-6-methylbenzamide; and

2-[(4-quinolyl)methyl]amino-N-(4-chloromethylphenyl)benzamide;

or a pharmaceutically acceptable salt thereof.

5. A compound of formula I according to any one of claims 1 to 4, or a pharmaceutically acceptable salt of such a compound, for use in a method for the treatment of the human or animal body.

6. A pharmaceutical preparation, comprising a compound of formula I according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier.

7. Use of a compound of formula I according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical product for the treatment of a disease which responds to an inhibition of angiogenesis.

8. Use of a compound of formula I according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical product for the treatment of a disease which responds to an inhibition of VEGF-receptor tyrosine kinase.

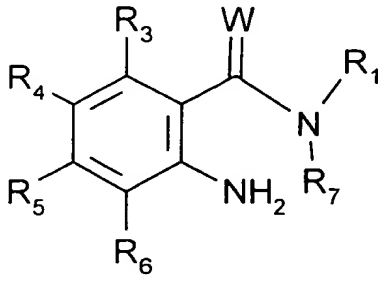
9. Use of a compound of formula I according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for the treatment of a disease which responds to an inhibition of VEGF-receptor kinase.

10. A pharmaceutical preparation which is suitable for administration to a warm-blooded animal, especially suffering from a disease which responds to an inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, comprising an effective quantity of a compound of formula I, or a pharmaceutically acceptable salt thereof, if salt-forming groups are present, according to claim 1, together with at least one pharmaceutically acceptable carrier.

11. A method for the treatment of a disease which responds to an inhibition of VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, which comprises administering a compound of formula I, or a pharmaceutically acceptable salt thereof, according to claim 1 in a quantity effective against the said diseases, to a warm-blooded animal requiring such treatment in a quantity suitable for the treatment of the said disease.

12. A process for the preparation of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, characterized in that

a) for the synthesis of a compound of the formula I wherein X represents NR_8, where R_8 is hydrogen and Y represents CHR_9-$(CH_2)_n$, each as indicated for a compound of formula I, and the remaining symbols W, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined for a compound of the formula I, an aniline derivative of the formula II



(II)

wherein W, R_1, R_3, R_4, R_5, R_6 and R_7 are as defined for a compound of the formula I, is reacted with a carbonyl compound of the formula III

$$R_2\text{-}(CH_2)_n\text{-}\ C(R_9)=O \qquad \text{(III)}$$

wherein n, R_2 and R_9 are as defined for a compound of the formula I in the presence of a reducing agent; or

b) for the synthesis of a compound of the formula I wherein X is C(=O) or SO_2 and the remaining symbols R_1, R_2, R_3, R_4, R_5, R_6, R_7, W and X are as defined for a compound of the formula I, an aniline derivative of the formula II as defined under process variante a) is reacted with an acid of the formula IV

$$R_2\text{-}X\text{-}OH \qquad \text{(IV)}$$

or a reactive derivative thereof;

where the starting compounds defined in a) or b) may also be present with functional groups in protected form if necessary and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible;

any protecting groups in a protected derivative of a compound of the formula I are removed; and, if so desired, an obtainable compound of formula I is converted into another compound of formula I, a free compound of formula I is converted into a salt, an obtainable salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.